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Review Article

Carcinoma of the gall bladder

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ABSTRACT

Gallbladder carcinoma is fifth most common gastrointestinal malignancy. Main indication for cholecystectomy is gallstone disease. Majority of gallbladder carcinomas are diagnosed during the course of histopathological evaluation of specimens obtained at cholecystectomy. Accomplishing radical cholecystectomy is advisable in these patients. Technically difficult gallbladder dissection during the course of laparoscopic surgery should raise a high suspicion of malignancy. Specimen retrieval bags should be used in all cases to avoid external spillage of bile giving rise to port side metastasis. A good outcome depends on prompt diagnosis and radical surgical resection. It is essential for a general surgeon to be aware of predisposing factors, pathology, patterns of presentation, and surgical options in gallbladder carcinoma.

Keywords: Gall bladder, Cancer, Risk factors, Treatment

INTRODUCTION

Gallbladder carcinoma is fifth most common GI neoplasm in the world. It is one of most common biliary tract malignancies. Poor prognosis is related to delay in diagnosis due to nonspecific symptoms in majority of patients. Gallbladder carcinoma is found in 0.2-3% of all cholecystectomy and 0.9-2% of all laparoscopic cholecystectomy specimens.[1] It picked up pre-operatively in only 30% of cases. Hence due to delay in diagnosis, outcome is extremely poor. In India it is commonly seen in Eastern UP, Western Bihar, Gangetic belt.[1,2] This is attributable to environmental factors, water pollutants, industrial and agricultural toxins containing aromatic hydrocarbons, nitrous amines and chemicals such as nitrates and nitrites which are products from domestic sewage.

RISK FACTORS

Gallstones continue to be the most important risk factor in aetiology of gallbladder carcinoma.[1] Increasing stone size increases risk of developing gallbladder carcinoma. Gallstones greater than 3 cm in size are associated with 10-fold increase in cancer. Type of stone, especially cholesterol stones which are associated with mucosal irritation and chronic inflammation are associated with high risk of cancer. Chronic inflammation causes DNA damage, thereby provoking repeated tissue proliferation and restoration attempts. This causes release of cytokines and growth factors pre-disposing to oncogenic transformation.

Porcelain gallbladder is a rare type of chronic inflammation with diffused transmural calcification. It has extremely high carcinogenic risk.[2] Similarly, xantho-granulomatous cholecystitis is also associated with gallbladder cancer.[2]

Chronic bacterial infection of biliary tract specially with *S. typhi* and *Helicobacter* species associated with gall-bladder cancer. Bacterial colonization causes degradation of bile, chronic irritation and inflammation of biliary wall. These changes may induce malignant transformation by altering tumour suppressor genes/ proto-oncogenes.[3]

Primary sclerosing cholangitis is a chronic inflammatory syndrome with a neoplastic field effect. It is associated with high incidence of gallbladder carcinoma. High incidence of gallbladder carcinoma is by virtue of metaplasia-dysplasia carcinoma sequence.[3]

Other risk factors include environmental exposure to toxins, obesity, metabolic syndrome, and diabetes. Gallbladder polyps are at high risk of malignancy if they are >10 mm in diameter and sessile while pseudo polyps and cholesterol polyps carry low risk. Overall, any polyp greater than 3 mm size, age of patient greater than 60 years, and increase in duration of existence of gallstones is associated with high incidence of malignancy.[3]

Abnormal junction of pancreatico biliary duct which is congenital in origin and is associated with development of papillary carcinoma. All papillary carcinomas are K-ras positive. They are more responsive to EGFR tyrosine kinase inhibitors.[4] Few gallbladder carcinomas are detected incidentally after evaluation of gallbladder specimens following cholecystectomy. They are designated as incidental or occult gallbladder carcinomas.

PATHOLOGY

Adenocarcinoma is the most common histological types seen in 80% of gallbladder carcinomas.[5] Gallstones is a common accompaniment of carcinoma of the gall bladder (Figure 1). Undifferentiated carcinomas are 6% and squamous carcinomas are 3%.

Figure 1: Malignant growth of the gall bladder with concomitant gall stones.

CLINICAL FEATURES

Majority of gallbladder carcinomas are asymptomatic for a long time but may present with nonspecific symptoms. In most of cases, symptoms are associated with gall stones. In few patients, symptoms include pain, anorexia, weight loss, jaundice, fever, vomiting, gallbladder mass, enlarged liver and asities.[6]

INVESTIGATION

Liver function test will reveal raised alkaline phosphatase and gamma glutamine transpeptidase. Total bilirubin maybe raised in cases where bile duct is compromised.[6] USG is suggestive, revealing gall stones in gallbladder with thickening of the gall bladder wall. CT scan is advantageous in confirming the pathology. It will reveal thickening of gallbladder wall, calcifications, gall stones, extrinsic compression of bile duct, infiltration into the liver bed, lymph node enlargement, and ascites. ERCP may be of help only in cases with jaundice. However, most of these cases are inoperable. CT guided FNAC provides 90% sensitivity and 100% specificity in diagnosing gallbladder masses. EUS may detect early lesions and better assessment of local infiltration.[7]

DIAGNOSIS

Majority of patients suffering from gallbladder carcinomas are diagnosed after routine histopathological evaluation of specimens following cholecystectomy for gallstone disease, typically described as incidental or occult gallbladder carcinoma. Difficulty while dissecting the gallbladder during the course of laparoscopic surgery should serve as a high index of suspicion for malignancy. In such cases, conversion to open with frozen section and lymph node biopsy is advisable. Transabdominal ultrasound is the initial modality for investigation. EUS helps in local staging of the disease. CECT however continues to be best modality for diagnosis and staging. MR cholangiography along with MR angiography helps in accurately determining vascular invasion. PET CT plays a role in determining metastatic disease.

STAGING

Management at prognosis of gallbladder carcinoma depends upon the staging (Table 1).[1,2,8]

Table 1: AJCC-UICC tumour-node-metastasis (TNM) classification.[8]

S. no.	Classification
1	**Primary tumour (T)**
	Tx primary tumour cannot be assessed
	T0 No evidence of primary tumour
	Tis carcinoma *in situ*
	T1 Tumour invades mucosa or muscle layer
	a Tumour invades mucosa
	b Tumour invades mucosal layer

Continued.

S. no.	Classification
	T2 Tumour invades peri muscular connective tissue; no extension beyond serosa or into liver
	T3 Tumour perforates serosa (visceral peritoneum) or directly invades into one adjacent organ/both (extension 2 cm or less into liver)
	T4 Tumour extends more than 2 cm into liver and/or two or more adjacent organs (Stomach, duodenum, colon, pancreas, Omentum, extrahepatic bile ducts, any involvement of liver)
2.	**Regional Lymph Nodes (N)**
	NX Regional lymph nodes cannot be assessed
	N0 No regional lymph node metastasis
	N1 Metastasis in cystic, peri choledochal and/or hilar lymph nodes (i.e., in the hepatoduodenal ligament) N2 Metastasis in peripancreatic (head only), peri duodenal, periportal, coeliac and/or superior mesenteric lymph nodes
3.	**Distant metastasis (M)**
	MX Presence of distant metastasis cannot be assessed
	M0 No distant metastasis
	M1 Distant metastasis

MANAGEMENT

The extent of primary tumor invasion (T) is the main determinant of surgical approach. The main objective of the surgery is to achieve R0 resection.[9-11]

Five-year survival after R0 resection is between 21-69% whereas survival is 0% in a patient with residual disease.[11-13] The type of liver resection varies from non-anatomical resection of segment 4B and 5 to right hepatectomy.

Regional lymphadenectomy is also an integral part of surgical intervention.[14,15]

Two types of lymphatic clearances based on the location of lymph nodes have been described.

N1-This includes lymph nodes in the hepatoduodenal ligament (cystic duct and hilar lymph node), N2-includes peripancreatic, periductal, periportal, common hepatic artery and superior mesenteric artery lymph nodes.

Laparoscopic cholecystectomy is strongly contraindicated whenever a gall bladder cancer is suspected preoperatively.[16-18] Such a patient should undergo formal radical cholecystectomy with intraoperative confirmation of diagnosis by frozen section. In a patient with incidentally diagnosed gall bladder cancer during laparoscopic cholecystectomy (0.3-3%), a second radical completion surgery is essential to complete the resection in conformity with oncological principles. However, Tis and T1a lesions may not require completion surgery.[19,20]

Port site recurrences develop in patients in whom unsuspected gall bladder cancer is discovered at the time of surgery. In such situations excision of the port site during the radical reoperation is necessary.[20]

For Tis and T1a lesions simple cholecystectomy will suffice giving a 100% five-year survival rate.[21] For T1B lesions where the tumor has invaded the muscular layer there is a high chance for recurrence and metastasis. Such lesions require radical cholecystectomy which include removal of 3 cm adjacent liver parenchyma (Segment 4B and 5) in addition to adequate lymphadenectomy. This provides a good 10-year survival rate. For T2 lesion in which there is invasion of peri muscular connective tissue with no extension into serosa or liver a radical formal resection of segment 4B and 5 is done. For T3 lesions involving the serosa, liver or adjacent organs a right hepatectomy with caudate lobectomy, regional lymphadenectomy and removal of affected structure is necessary.[22] For T4 lesion with vascular, lymphatic dissemination and metastasis it is not surgically possible to achieve R0 resection. Such a patient is therefore considered for palliative care comprising of pain control accompanied with surgical or endoscopic biliary drainage.[23] For advanced gall bladder cancer, no surgical intervention should be contemplated as it will not be possible to achieve a R0 resection.[24]

Adjuvant therapy is only applicable to advanced stage disease, as there is no therapeutically proven adjuvant therapy. However, 3 agents maybe tried which include: gemcitabine, fluorouracil and platinum compound.[7,8,25] A combination therapy comprising of gemcitabine and cisplastin yields better results. The role of radiotherapy is limited in gall bladder cancer. Targeted therapy against epidermal growth factor receptor has anti-proliferative effect in vitro. However, this therapy continues to be in experimental stage.[26]

CONCLUSION

Survival outcome is poor in gallbladder carcinoma as the T stage advances. Incidental or occult gallbladder carcinoma continues to be relatively common. Completion radical cholecystectomy is essential in these cases depending on the staging. Laparoscopic cholecystectomy is contraindicated in preoperatively suspect cases of gall bladder cancer.

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